Final Recommendation Statement

Prevention of Human Immunodeficiency Virus (HIV) Infection: Preexposure Prophylaxis

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Recommendation Summary

Population	Recommendation	Grade (What's This?)
Persons at high risk of HIV acquisition	The USPSTF recommends that clinicians offer preexposure prophylaxis (PrEP) with effective antiretroviral therapy to persons who are at high risk of HIV acquisition.	A

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To read the evidence summary in *JAMA*, select hereThis link goes offsite. Click to read the external link disclaimerThis link goes offsite. Click to read the external link disclaimer.

See the Clinical Considerations section for information about identification of persons at high risk and selection of effective antiretroviral therapy.

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Preface

The US Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision makin the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and har

Rationale

Importance

An estimated 1.1 million individuals in the United States are currently living with HIV,[1] and more than 700,000 persons have died of AIDS since the first cases were reported 1981.[2] In 2017, there were 38,281 new diagnoses of HIV infection reported in the United States; 81% (30,870) of these new diagnoses were among males and 19% (7312) were among females.[2] Although treatable, HIV infection has no cure and has significant health consequences.

Identification of Risk Status

Although the USPSTF found inadequate evidence that specific risk assessment tools can accurately identify persons at high risk of HIV acquisition, it found adequate epidemiologic data on risk factors that can be used to identify persons at high risk of acquiring HIV infection.

Benefits of Preventive Medication

The USPSTF found convincing evidence that PrEP is of substantial benefit for decreasing the risk of HIV infection in persons at high risk of HIV infection, either via sexual acquisition or through injection drug use. The USPSTF also found convincing evidence that adherence to PrEP is highly correlated with its efficacy in preventing the acquisiti of HIV infection.

Harms of Preventive Medication

The USPSTF found adequate evidence that PrEP is associated with small harms, including kidney and gastrointestinal adverse effects.

USPSTF Assessment

The USPSTF concludes with high certainty that the net benefit of the use of PrEP to reduce the risk of acquisition of HIV infection in persons at high risk of HIV infection is substantial.

Clinical Considerations

Patient Population Under Consideration

Patient Population Under Consideration

This recommendation applies to persons who are not infected with HIV and are at high risk of HIV infection.

Assessment of Risk

Although the USPSTF found no well-validated, accurate tools to assess risk of HIV acquisition, epidemiologic data, Centers for Disease Control and Prevention (CDC) guidelines,[3] and enrollment criteria for clinical trials provide guidance on detecting persons who may be at high risk. Persons at risk of HIV infection include men who have s with men, persons at risk via heterosexual contact, and persons who inject drugs. Within these groups, certain risk factors or behaviors (outlined below) can place persons a high risk of HIV infection.

It is important to note that men who have sex with men and heterosexually active persons are not considered to be at high risk if they are in a mutually monogamous relation with a partner who has recently tested negative for HIV. In addition, all persons being considered for PrEP must have a recently documented negative HIV test result.

The USPSTF recommends that the following persons be considered for PrEP:

1. Men who have sex with men, are sexually active, and have 1 of the following characteristics:

- A serodiscordant sex partner (ie, in a sexual relationship with a partner living with HIV)
- Inconsistent use of condoms during receptive or insertive anal sex
- A sexually transmitted infection (STI) with syphilis, gonorrhea, or chlamydia within the past 6 months

2. Heterosexually active women and men who have 1 of the following characteristics:

- A serodiscordant sex partner (ie, in a sexual relationship with a partner living with HIV)
- Inconsistent use of condoms during sex with a partner whose HIV status is unknown and who is at high risk (eg, a person who injects drugs or a man who has sex with and women)
- An STI with syphilis or gonorrhea within the past 6 months

3. Persons who inject drugs and have 1 of the following characteristics:

- Shared use of drug injection equipment
- Risk of sexual acquisition of HIV (see above)

Persons who engage in transactional sex, such as sex for money, drugs, or housing, including commercial sex workers or persons trafficked for sex work, constitute another group at high risk of HIV acquisition and should be considered for PrEP based on the criteria outlined above. Men who have sex with men and women are at risk of HIV acquisition and should be evaluated for PrEP according to the criteria outlined above for men who have sex with men and heterosexually active men.

Transgender women and men who are sexually active may be at increased risk of HIV acquisition and should be considered for PrEP based on the criteria outlined above. Transgender women are at especially high risk of HIV acquisition. The CDC estimates that approximately one-fourth of transgender women are living with HIV, and more tha half (an estimated 56%) of black/African American transgender women are living with HIV.[4] Although trials of PrEP enrolled few transgender women and no trials have been conducted among transgender men, PrEP has been shown to reduce the risk of HIV acquisition during receptive and insertive anal and vaginal sex. Therefore, its use may b considered in all persons (cisgender and transgender) at high risk of sexual acquisition of HIV.

Consistent use of condoms decreases risk of HIV acquisition by approximately 80%[5] and also decreases the risk of other STIs. However, sexually active adults often use condoms inconsistently.[6] PrEP should be considered as an option to reduce the risk of HIV acquisition in persons who use condoms inconsistently, while continuing to encourage and support consistent condom use.

To date, in 3 studies, transmission of HIV to a seronegative partner from a partner living with HIV has not been observed when the seropositive partner was being treated wit antiretroviral therapy and had a suppressed viral load.[7-9] It is not known whether PrEP use further decreases the risk of HIV transmission when a seropositive partner has a documented undetectable viral load.

The risk of acquisition of HIV infection is on a continuum. This risk depends on the likelihood that a specific act or activity will transmit HIV and the likelihood that a sex partne drug injection partner is living with HIV. The likelihood of HIV transmission is highest with needle-sharing injection drug use and condomless receptive anal intercourse, wher condomless insertive anal sex and condomless receptive and insertive penile-vaginal sex have a risk of transmission that is approximately 10- to 15-fold lower than receptive anal intercourse.[5] One recent study estimated the prevalence of HIV (ie, the likelihood that a partner whose HIV status is unknown is living with HIV) as 12.4% among men w have sex with men and 1.9% among persons who inject drugs,[10] although an earlier systematic review estimated the prevalence of HIV among persons who inject drugs to b much higher (16%).[11] The prevalence of HIV among men who have sex with men and women is estimated to be intermediate between that of men who have sex with men a heterosexually active men.[12] Thus, persons at high risk of HIV acquisition via penile-vaginal intercourse, including those with a recent bacterial STI acquired via penile-vagin intercourse, will generally be at lower absolute risk than persons at high risk via receptive anal intercourse or injection drug use. These are factors that clinicians and patients can consider as they discuss the use of PrEP for HIV prevention.

In addition, risk behaviors should be interpreted in the context of the HIV prevalence in a community or network; that is, risk behaviors in a high-prevalence setting carry a hig risk of acquiring HIV infection than the same behaviors in a low-prevalence setting. The threshold of HIV prevalence below which PrEP has insignificant net benefit is not kno

Preventive Medication

Once-daily oral treatment with combined tenofovir disoproxil fumarate and emtricitabine is the only formulation of PrEP approved by the US Food and Drug Administration (F for use in the United States in persons at risk of sexual acquisition of HIV infection. However, several studies reviewed by the USPSTF found that tenofovir disoproxil fumara alone was also effective as PrEP, and CDC guidelines note that, given these trial data, tenofovir disoproxil fumarate alone can be considered as an alternative regimen for hi risk heterosexually active men and women and persons who inject drugs.[3]

According to its product label, tenofovir disoproxil fumarate/emtricitabine may be considered for use as PrEP during pregnancy.[13] No trials of oral PrEP included pregnant women; however, pregnancy is associated with an increased risk of HIV acquisition.[14] CDC guidelines recommend shared decision making for pregnant women who are considering starting or continuing PrEP during pregnancy.

Adolescents at high risk of HIV acquisition could benefit from PrEP, and tenofovir disoproxil fumarate/emtricitabine is approved by the FDA for use as PrEP in adolescents wh weigh at least 35 kg.[13] In addition, young men who have sex with men are at particularly high risk of HIV acquisition.[15] However, no randomized clinical trials (RCTs) of PrEP enrolled adolescents. Limited data suggest that PrEP use is not associated with significant adverse events in adolescents but may be associated with slightly less bone mine accrual than would be expected.[16] The USPSTF suggests that clinicians weigh all these factors when considering PrEP use in adolescents at high risk of HIV acquisition. In addition, clinicians need to be aware of any local laws and regulations that may apply when providing PrEP to an adolescent minor.

Additional Approaches to Prevention

Several additional approaches for decreasing risk of HIV acquisition are also available. Consistent use of condoms decreases risk of HIV acquisition by approximately 80%[5]

reduces the risk of other STIs. The USPSTF recommends intensive behavioral counseling to reduce behaviors associated with increased risk of STIs and HIV acquisition an increase condom use among adolescents and adults at increased risk of STIs.[17] The CDC has made several recommendations, including abstinence, reducing one's numbe sex partners, and consistent condom use, to decrease risk of STIs, including HIV.[18] The CDC also recommends syringe service programs (ie, needle exchange programs) to reduce the risk of HIV acquisition and transmission among persons who inject drugs.[19] The Community Preventive Services Task Force has also issued several recommendations on the prevention of HIV and other STIs.[20] Postexposure prophylaxis, started as soon as possible after a possible exposure event, can also decrease the of HIV infection.

Screening for HIV infection to detect undiagnosed cases and antiretroviral treatment in persons living with HIV to suppress viral load are both important approaches to decreasing the risk of HIV transmission at the population level, while also benefiting the individual living with HIV. The USPSTF recommends screening for HIV infection in adolescents and adults aged 15 to 65 years, younger adolescents and older adults at increased risk, and all pregnant persons.[21]

Useful Resources

The CDC guidelines on PrEP for the prevention of HIV infection are available at https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdfThis link goes offsite. Click to read the external link disclaimerThis link goes offsite. Click to read the external link disclaimer[3] and https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-provider-supplement-2017.pdfThis link goes offsite. Click to read the external link disclaimerThis link goes offsite. Click to read the external link disclaimer.[22] Additional CDC resource on PrEP for both clinicians and consumers are available at https://www.cdc.gov/hiv/risk/prep/index.htmlThis link goes offsite. Click to read the external link disclaimerThis link goes offsite. Click to read the external link disclaimer.[23] Community-level HIV prevalence data for the United States are available at https://www.cdc.gov/nchhstp/atlasThis li goes offsite. Click to read the external link disclaimerThis link goes offsite. Click to read the external link disclaimer.[24] The USPSTF has issued recommendations on behavio counseling to reduce risk of STIs[17] and on screening for HIV infection.[21]

Other Considerations

Implementation

The first step in implementing PrEP is identifying persons at high risk of HIV acquisition who may benefit from PrEP. However, identifying persons at risk of HIV can be challenging because of stigma and discrimination against gay, bisexual, transgender, and nonbinary persons, or the lack of a trusting relationship between the patient and clinician. It is important that clinicians routinely take a sexual and injection drug use history for all their patients in an open and nonjudgmental manner. If a person is identifie potentially belonging to a high-risk group, then further discussion can identify behaviors that may make that person an appropriate candidate for PrEP.

The CDC provides a complete discussion of implementation considerations for PrEP, including baseline and follow-up testing and monitoring, time to achieving protection, a discontinuing PrEP.[3] A few particularly important points regarding the provision of PrEP are outlined below.

Before prescribing PrEP, clinicians should exclude persons with acute or chronic HIV infection through taking a medical history and HIV testing. The 2-drug antiretroviral regi used in PrEP, when used alone, is not an effective treatment for HIV infection, and its use in persons living with HIV can lead to the emergence of, or selection for, drug-resis HIV infection. It is also generally recommended that kidney function testing, serologic testing for hepatitis B and C virus, testing for other STIs, and pregnancy testing (when appropriate) be conducted at the time of or just before initiating PrEP. Ongoing follow-up and monitoring, including HIV testing every 3 months, is also suggested. The time fr initiation of PrEP to achieving protection against HIV infection is unknown. Pharmacokinetic data suggest that maximum levels of tenofovir diphosphate (the active form of tenofovir) is reached in 7 days in rectal tissue and in 20 days in blood (peripheral blood mononuclear cells) and vaginal tissue.[3] Patients can continue PrEP as long as high r of HIV acquisition continues. Patients may discontinue PrEP for several reasons, including personal preference, decreased risk of HIV acquisition, or adverse medication eff

PrEP does not reduce the risk of other STIs. Consistent use of condoms decreases risk of HIV acquisition by approximately 80%[5]and reduces the risk of other STIs. Promot consistent condom use is an important component of a successful PrEP program. The CDC also recommends regular screening for STIs in men who have sex with men wh are at high risk of STIs, and testing in anyone with signs or symptoms.[3]

Clinical trials demonstrate a strong connection between adherence to PrEP and its effectiveness in preventing HIV acquisition. Reduced adherence is associated with marke declines in effectiveness. Therefore, adherence support is a key component of providing PrEP. Components of adherence support include establishing trust and open communication with patients, patient education, reminder systems for taking medication, and attention to medication adverse effects and having a plan to address them. Additional information on adherence support is available from the CDC guidelines.[3, 22] Adherence support is especially important in populations shown to have lower adhere to PrEP, such as young persons and racial/ethnic minorities.[25-27]

It is important for clinicians to recognize that barriers to the implementation and uptake of PrEP exist. These barriers can include structural barriers, such as lack of health insurance, and other factors, such as an individual's willingness to believe that he or she is an appropriate candidate for PrEP or to take PrEP. There are also racial/ethnic disparities in the use of PrEP. One study reported that although black/African American persons account for an estimated 44% of all new HIV infections in the United States, only 10.1% of those who initiated PrEP from 2012 to 2015 were black/African American. Similarly, black women, who are also disproportionately affected by HIV, were more than 4 times less likely to have initiated PrEP than white women.[28] These barriers and disparities need to be addressed to achieve the full benefit of PrEP.

Research Needs and Gaps

Research is needed to develop and validate tools that are highly accurate for identifying persons at high risk of HIV acquisition who would benefit from PrEP. When develope and validated, risk assessment instruments should include those populations most at risk of HIV infection, particularly racial/ethnic minorities such as black/African American and Hispanic/Latino populations.

Research is needed on different drug regimens and dosing strategies for PrEP. Several trials investigating different antiretroviral drugs or drug regimens for use as PrEP are ongoing.

Research is needed on factors associated with adherence to PrEP and methods to increase uptake and adherence, especially in populations with lower use of and adherenc PrEP, such as younger persons and racial/ethnic minorities.

Trials or demonstration projects of PrEP in US populations of heterosexual persons, persons who inject drugs, and transgender women and men are needed to better quanti effectiveness in those populations. Research is needed on the safety and effectiveness of PrEP during pregnancy and breastfeeding. Additional research is needed to deter whether the use of PrEP is associated with an increased risk of other STIs. Research is also needed on the long-term safety and effectiveness of PrEP.

Discussion

Burden of Disease

Since the first cases of AIDS were reported in 1981, more than 700,000 persons in the United States have died of AIDS.[2] The CDC estimates that 1.1 million individuals in th United States are currently living with HIV infection,[1] including an estimated 15% who are unaware of their infection.[10] The annual number of new HIV infections in the Unite States has decreased from about 41,200 new cases in 2012 to 38,300 in 2017.[2] Of these new cases of HIV infection in 2017, 81% were among males and 19% were among females.[2] Groups disproportionately affected by HIV infection in the United States include men who have sex with men, black/African American populations, and Hispanic/La

populations. From 2012 to 2017, HIV incidence rates increased among persons aged 25 to 29 years and among American Indian/Alaska Native and Asian populations.[2]

PrEP is currently not used in many persons at high risk of HIV infection. The CDC estimates that approximately 1.2 million persons were eligible for PrEP in 2015 (492,000 m who have sex with men, 115,000 persons who inject drugs, and 624,000 heterosexually active adults),[29] and a recent study estimates that 100,282 persons were using PrEP 2017.[30]

Scope of Review

For this recommendation, the USPSTF commissioned a systematic review[31, 32] of the evidence on the benefits of PrEP for the prevention of HIV infection with oral tenofovir disoproxil fumarate monotherapy or tenofovir disoproxil fumarate/emtricitabine (referred to simply as "PrEP" hereafter) and whether the benefits vary by risk group, populatio subgroup, or regimen or dosing strategy; the diagnostic accuracy of risk assessment tools to identify persons at high risk of HIV acquisition; the rates of adherence to PrEP i primary care settings; the association between adherence and effectiveness of PrEP; and the harms of PrEP when used for HIV prevention.

Effectiveness of Risk Assessment

The USPSTF found 7 studies that evaluated risk assessment tools developed in US cohorts for predicting incident HIV infection—6 studies in men who have sex with men[33] and 1 study in persons who inject drugs.[39] The USPSTF found no studies in US cohorts evaluating tools for predicting risk of HIV infection in men and women at increased r of HIV infection via heterosexual contact. In those studies that reported it, discrimination of the risk prediction instrument was moderate, with an area under the receiver operating characteristic curve of 0.66 to 0.72. However, each study evaluated a different risk prediction tool. Some instruments were not validated in independent cohorts, ar several instruments were developed and validated using older (ie, before 2000) cohorts. Most of the studies of risk prediction tools in men who have sex with men were developed in predominantly white populations, and 2 studies found that several of the instruments performed more poorly in black men who have sex with men (area under t receiver operating characteristic curve, 0.49-0.63).[37, 38] All tools are predicated on knowing that a person belongs to an HIV risk group; no tool has been designed to predict incident HIV infection in persons not already identified as belonging to an HIV risk group.[31]

The USPSTF considered several factors in its assessment of risk of HIV acquisition, including the prevalence of HIV infection within a group and the risk that a specific beha or action will lead to acquisition of HIV infection. As discussed in the Assessment of Risk section, 1 study estimated the prevalence of HIV infection among men who have se with men to be 12.4%; persons who inject drugs, 1.9%; and the overall population 13 years and older, 0.4%,[10] although another study estimated a significantly higher prevalence (16%) among persons who inject drugs.[11] In terms of risk of HIV acquisition from specific behaviors, receptive anal intercourse without a condom and needle-sha injection drug use carry the highest risk, whereas insertive anal intercourse, receptive penile-vaginal intercourse, and insertive penile-vaginal intercourse carry lower but not negligible risks of acquiring HIV from a partner or source who is seropositive for HIV.[5]

Effectiveness of Preventive Medication

The USPSTF found 12 RCTs that evaluated the effect of PrEP vs placebo[25, 40-49] or no PrEP[50] on the risk of HIV acquisition. One trial was of fair quality because of an open label design; all other trials were of good quality. Duration of follow-up ranged from 4 months to 4 years. Six trials[42-44, 47-49] enrolled men and women at increased risk of HIV infection via heterosexual contact, 4 trials[25, 40, 46, 50] enrolled men who have sex with men or transgender women, 1 trial[41] enrolled high-risk women and men who have sex with men, and 1 trial[45] enrolled persons who inject drugs. No trial enrolled pregnant women or persons younger than 18 years. Three trials[25, 45, 47] evaluated tenofovir disop fumarate (300 mg), 7 trials[40-42, 46, 48, 49] evaluated tenofovir disoproxil fumarate (300 mg)/emtricitabine (200 mg), 1 trial[50] evaluated tenofovir disoproxil fumarate (245 mg)/emtricitabine (200 mg), and 2 trials[43, 44] included study groups for both tenofovir disoproxil fumarate (300 mg) alone and tenofovir disoproxil fumarate (300 mg)/emtricitabine (200 mg). PrEP was prescribed daily in 11 trials,[25, 41-50] and dosing was intermittent or event-driven in 3 trials (including 2 trials that also included daily dos groups).[40-42] Seven trials were conducted in Africa,[41-44, 47-49] 1 in Thailand,[45] 2 in Europe or Canada,[40, 50] and 1 in the United States;[25] 1 trial was multinational.[46] All trials persons at high risk of HIV infection via heterosexual contact were conducted in Africa, and the only trial of persons who inject drugs was conducted in Thailand.[45] All trials o PrEP also included behavioral and adherence counseling, and most specified providing condoms to all trial participants.

One small trial reported no cases of HIV infection.[42] In the other 11 trials, the rate of HIV infection ranged from 1.4% to 7.0% over 4 months to 4 years in participants random assigned to placebo or no PrEP and from 0% to 5.6% in those randomly assigned to PrEP. In a meta-analysis of these trials, PrEP was associated with reduced risk of HIV infection compared with placebo or no PrEP (relative risk [RR], 0.46 [95% CI, 0.33-0.66]; absolute risk reduction, −2.0% [95% CI, −2.8% to −1.2%]) after 4 months to 4 years[32]

PrEP was effective across population subgroups defined by HIV risk category. There were no statistically significant differences in estimates of effectiveness for PrEP vs plac or no PrEP in risk of HIV acquisition when trials were stratified according to whether they enrolled men who have sex with men or transgender women (although the number transgender persons in trials was small) (4 trials; RR, 0.23 [95% CI, 0.08-0.62]), men and women at increased risk of HIV infection via heterosexual contact (5 trials; RR, 0.5 [95% CI, 0.31-0.97]), or persons who inject drugs (1 trial; RR, 0.52 [95% CI, 0.29-0.92]; $P = 0.43$ for interaction).[31, 32]

In a meta-analysis of the trials reviewed by the USPSTF, both tenofovir disoproxil fumarate/emtricitabine and tenofovir disoproxil fumarate alone appeared equally effective i decreasing the risk of HIV acquisition (8 trials; RR, 0.44 [95% CI, 0.27-0.72] and 5 trials; RR, 0.49 [95% CI, 0.28-0.84], respectively; $P = 0.79$ for interaction).[31, 32]

Three included trials investigated alternative dosing strategies (using PrEP less frequently than daily [intermittent dosing] or before and after HIV exposure events [event-driv dosing]).[40-42] One trial[42] reported no HIV events, and a second[41] did not report results for intermittent and daily dosing of PrEP groups separately. The third trial (Interventio Préventive de l'Exposition aux Risques avec et pour les Gays) found that event-driven PrEP dosing was associated with a lower risk of HIV infection compared with placebo men who have sex with men (RR, 0.14 [95% CI, 0.03-0.63]).[40] In that trial, men randomly assigned to PrEP took an average of about 4 doses of PrEP per week (15 doses p month), so it is uncertain whether this finding would apply to less frequent use of event-driven dosing. In addition, tenofovir disoproxil fumarate accumulates more rapidly in a tissue than vaginal tissue,[51] so this study may not be generalizable to other risk groups.

The USPSTF also evaluated the evidence on the relationship between adherence to PrEP and its effectiveness in decreasing risk of HIV infection. Methods for evaluating adherence differed between studies and included patient diaries and self-report, pill counts, adherence monitoring devices, drug levels (eg, plasma or dried blood spots), and prescription fill data.

In the trials of PrEP reviewed by the USPSTF, adherence to PrEP ranged from 30% to 100%, and the RR of HIV infection in participants randomly assigned to PrEP, compar with placebo or no PrEP, ranged from 0.95 to 0.07.[31, 32] In a stratified analysis of these studies, a strong interaction ($P < 0.00001$) between level of adherence and effectiven of PrEP was found, with higher levels of adherence associated with greater reduction in risk of HIV acquisition (adherence ≥70%: 6 trials; RR, 0.27 [95% CI, 0.19-0.39]; adherence >40% to <70%: 3 trials; RR, 0.51 [95% CI, 0.38-0.70]; and adherence ≤40%: 2 trials; RR, 0.93 [95% CI, 0.72-1.20]).[31, 32] There was also a strong association (P 0.0005) between adherence and effectiveness when adherence was analyzed as a continuous variable in a meta-regression.[31, 32]

Since the effectiveness of PrEP is closely tied to adherence, the USPSTF reviewed the evidence on levels of adherence to PrEP in US-relevant settings. Three observationa studies of US men who have sex with men found adherence to PrEP (based on tenofovir diphosphate levels in dried blood spot sampling consistent with ≥4 doses/wk) of 66 90% over 4 to 48 weeks.[27, 52, 53] Two observational studies of younger men who have sex with men (mean ages, 20 and 16 years) reported lower rates of adherence to PrE (based on blood spot sampling) of approximately 50% at 12 weeks, decreasing to 34% and 22% at 48 weeks.[16, 54] Two studies in US men who have sex with men found tha self-reported adherence correlated highly with adherence based on dried blood spot sampling.[25, 26]

Multivariate analysis of the largest US PrEP implementation study to date[53] found that black race was associated with lower adherence than white race (adjusted odds ratio, 0.28 [95% CI, 0.12-0.64]). Having stable housing or having receptive anal sex without a condom with 2 or more partners was associated with increased adherence (adjusted odds ratio, 2.02 [95% CI, 1.14-3.55] and 1.82 [95% CI, 1.14-2.89], respectively). There was no association between age, educational attainment, income level, health insura

status, and alcohol or drug use and adherence. Only 1.4% of participants enrolled were transgender women, so it is not possible to draw conclusions about adherence to PrE in this population. The USPSTF found no US studies on factors associated with adherence to PrEP in persons who inject drugs or persons at high risk of HIV infection via heterosexual contact.[31]

Potential Harms of Risk Assessment and Preventive Medication

The RCTs that investigated the effectiveness of PrEP had 4 months to 4 years of follow-up and also reported on the harms of PrEP.[25, 40-50, 55-62] In a pooled analysis of thes studies, PrEP was associated with increased risk of renal adverse events (primarily grade 1 or greater serum creatinine elevation) vs placebo (12 trials; absolute risk differen 0.56% [95% CI, 0.09%-1.04%]). There was no clear difference in risk of kidney adverse events when trials were stratified according to use of tenofovir disoproxil fumarate monotherapy or tenofovir disoproxil fumarate/emtricitabine. Serious renal events were rare, and no trial reported a difference between PrEP and placebo in risk of serious re events or withdrawals due to renal events.[31, 32] Six trials[41, 42, 55-58] evaluated whether renal adverse events while using PrEP were persistent. Three studies[55, 57, 58] report return to normal serum creatinine levels after cessation of PrEP, and 2 others[41, 42] reported normalization of creatinine level without PrEP cessation. In 1 trial, the Bangkok Tenofovir Study of persons who inject drugs, there were 7 cases of grade 2 or greater creatinine level elevation, and all but 1 case resolved after PrEP cessation.[56]

PrEP was associated with increased risk of gastrointestinal adverse events (primarily nausea) vs placebo (12 trials; absolute risk difference, 1.95% [95% CI, 0.48%-3.43%]). risk of gastrointestinal adverse events increased with both tenofovir disoproxil fumarate monotherapy and tenofovir disoproxil fumarate/emtricitabine,[31] with risk diminishing time in 3 trials.[45, 46, 48] Serious gastrointestinal events were rare in trials reporting this outcome, with no differences between PrEP and placebo.[44, 46-50]

Tenofovir disoproxil fumarate exposure is associated with bone loss,[48, 59-61] which could result in increased fracture risk. A meta-analysis of 7 studies that reported on fractu using both study data and updated fracture data reported to the FDA, found a statistically nonsignificant increased risk of fracture in persons randomly assigned to PrEP vs placebo. This result was also heavily weighted by the 1 study of PrEP in persons who inject drugs, which reported a relatively high fracture rate.[31, 32]

One concern about PrEP is that its use may lead to persons at risk of HIV acquisition not using condoms or engaging in other behaviors that could increase their risk of STIs behavioral risk compensation). In meta-analyses of the studies reviewed by the USPSTF, there were no differences between PrEP and placebo or no PrEP in risk of syphilis trials; RR, 1.08 [95% CI, 0.98-1.18]), gonorrhea (5 trials; RR, 1.07 [95% CI, 0.82-1.39]), chlamydia (5 trials; RR, 0.97 [95% CI, 0.80-1.18]), or combined bacterial STIs (2 trial RR, 1.14 [95% CI, 0.97-1.34]).[31, 32] All of the trials except for 1 were blinded, which could affect risk of STIs if participants who do not know if they are taking PrEP or placeb behave differently than those who know they are taking PrEP. In the 1 open-label trial, there was also no statistically significant association between PrEP and the risk of STI

An additional concern is the possibility that the use of antiretroviral drugs as PrEP could lead to the development or acquisition of drug-resistant HIV infection. In 8 trials of Pr using tenofovir disoproxil fumarate monotherapy or tenofovir disoproxil fumarate/emtricitabine, 3 of 282 patients (1.1%) newly diagnosed with HIV infection while taking PrEP had tenofovir resistance mutations.[40, 43-47, 49, 50] In 6 trials of PrEP with tenofovir disoproxil fumarate/emtricitabine, 14 of 174 patients (8.0%) newly diagnosed with HIV infection while taking PrEP had emtricitabine resistance mutations.[40, 43, 44, 46, 48-50] There was 1 case of multiple resistance mutations, which is included in the total number both tenofovir and emtricitabine resistance mutations. Most resistance mutations (1/2 tenofovir resistance mutations, 8/13 emtricitabine resistance mutations, and 1 case of multiple resistance mutations, or 63% of total cases) occurred in persons who were already infected with HIV on trial enrollment but were not recognized as such. This highli the importance of testing for HIV and excluding persons with acute or chronic HIV infection before initiating PrEP. The USPSTF found no data on the effect of resistance mutations on clinical outcomes.

No trial of oral PrEP enrolled pregnant women, and women who became pregnant during the course of the trials were withdrawn from participation. Three trials reported on pregnancy outcomes in women who were withdrawn from PrEP because of pregnancy.[41, 48, 62] Among women who became pregnant in the trials, PrEP was not associated increased risk of spontaneous abortion. One trial, the Partners PrEP trial, also found no differences between PrEP and placebo in pregnancy rate, risk of preterm birth, birth anomalies, or postpartum infant mortality.[62]

Estimate of Magnitude of Net Benefit

The USPSTF found convincing evidence that PrEP is of substantial benefit in decreasing the risk of HIV infection in persons at high risk of HIV acquisition. The USPSTF also found convincing evidence that adherence to PrEP is highly correlated with its efficacy in preventing the acquisition of HIV infection; thus, adherence to PrEP is central to realizing its benefit. The USPSTF found adequate evidence that PrEP is associated with small harms, including renal and gastrointestinal adverse effects. The USPSTF concludes with high certainty that the magnitude of benefit of PrEP with oral tenofovir disoproxil fumarate–based therapy to reduce the risk of acquisition of HIV infection in persons at high risk is substantial.

How Does Evidence Fit With Biological Understanding?

HIV is an RNA retrovirus that infects immune cells, in particular $CD4^+$ T cells. Antiretroviral agents interfere with 1 of several steps in viral infection and replication, such as H entry into CD4+ cells, reverse transcription of viral RNA into DNA, integration of the viral genome into the host genome, and assembly of HIV proteins and RNA into new viru Tenofovir disoproxil fumarate and emtricitabine are both reverse transcriptase inhibitors and have favorable safety profiles. Tenofovir disoproxil fumarate achieves particularly high concentrations in rectal tissue, and emtricitabine achieves high concentrations in the female genital tract.[64] The possibility of using PrEP to prevent HIV transmission wa suggested by the success of antiretroviral agents in preventing mother-to child transmission of HIV and their use as postexposure prophylaxis[65-67] and was demonstrated in several animal models, including 1 model showing that tenofovir disoproxil fumarate and emtricitabine decreased the risk of rectal transmission of simian immunodeficiency v in macaques.[68]

Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from November 20, 2018, to December 26, 2018. In response to public comment, the USPSTF clarified language describing risk groups and high-risk activities in the Clinical Considerations section. In the same section, the USPSTF also added information about the high burden of HIV in transgender women and the risk of HIV transmission in persons living with HIV who have a suppressed viral load. The USPSTF also added details on the likelihood that specific activities will lead to the transmission of HIV and on the prevalence of HIV in different groups. The USPSTF addres stigma, barriers to access to care, and racial/ethnic disparities as obstacles to the use of PrEP by persons and groups at high risk.

The USPSTF received comments requesting that it include a meta-analysis[69] examining the effects of PrEP on the risk of STIs in the evidence reviewed for this recommendation. In response, the USPSTF notes that it reviewed that particular meta-analysis; however, because of methodologic limitations of the studies included in the meta-analysis, such as not adjusting for differential STI testing rates and use of self-report to determine baseline STI rates, it was not included in the body of evidence considered for this recommendation. Last, the USPSTF added the American College of Obstetricians and Gynecologists committee opinion on the use of PrEP to the Recommendations of Others section.

Recommendations of Others

The 2017 CDC guidelines recommend PrEP with tenofovir disoproxil fumarate/emtricitabine as an HIV prevention option for men who have sex with men, heterosexually act men and women, and persons who inject drugs who are at substantial risk of HIV infection, with tenofovir disoproxil fumarate monotherapy as an alternative for heterosexual active men and women and persons who inject drugs and who are at substantial risk.[3] The American College of Obstetricians and Gynecologists suggests that, in combinati with other proven HIV-prevention methods, PrEP may be a useful tool for women at highest risk of HIV acquisition and that such women should be considered candidates fo PrEP.[70] 2016 World Health Organization guidance recommends offering PrEP containing tenofovir disoproxil fumarate as an additional prevention choice for persons at substantial risk of HIV infection (provisionally defined as HIV incidence higher than 3 cases/100 person-years) as part of HIV prevention approaches.[71]

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Authors followed the policy regarding conflicts of interest described at https://www.uspreventiveservicestaskforce.org/Page/Name/conflict-of-interest-disclosures. All members of the USPSTF receive tra reimbursement and an honorarium for participating in USPSTF meetings.

Funding/Support: The USPSTF is an independent, voluntary body. The US Congress mandates that the Agency for Healthcare Research and Quality (AHRQ) support the operations of the USPSTF.

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Current as of: June 2

Internet Citation: *Final Recommendation Statement: Prevention of Human Immunodeficiency Virus (HIV) Infection: Preexposure Prophylaxis*. U.S. Preventive Services Task Force. July 2
https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/prevention-of-human-immunodeficiency-virus-hiv-infection-pre-exposure-prophyl